11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S239–S251 | https://doi.org/10.2337/dc25-S011

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a Assess kidney function (i.e., spot urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] in people with type 1 diabetes with duration of ≥5 years and in all people with type 2 diabetes regardless of treatment. **B**

11.1b In people with established chronic kidney disease (CKD), monitor urinary albumin (e.g., spot UACR) and eGFR 1–4 times per year depending on the stage of the kidney disease (**Fig. 11.1**). **B**

Treatment

Recommendations

11.2 Optimize glucose management to reduce the risk or slow the progression of CKD (**Fig. 9.3**). **A**

11.3 Optimize blood pressure management (aim for <130/80 mmHg [**Fig. 10.2**]) and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. **A**

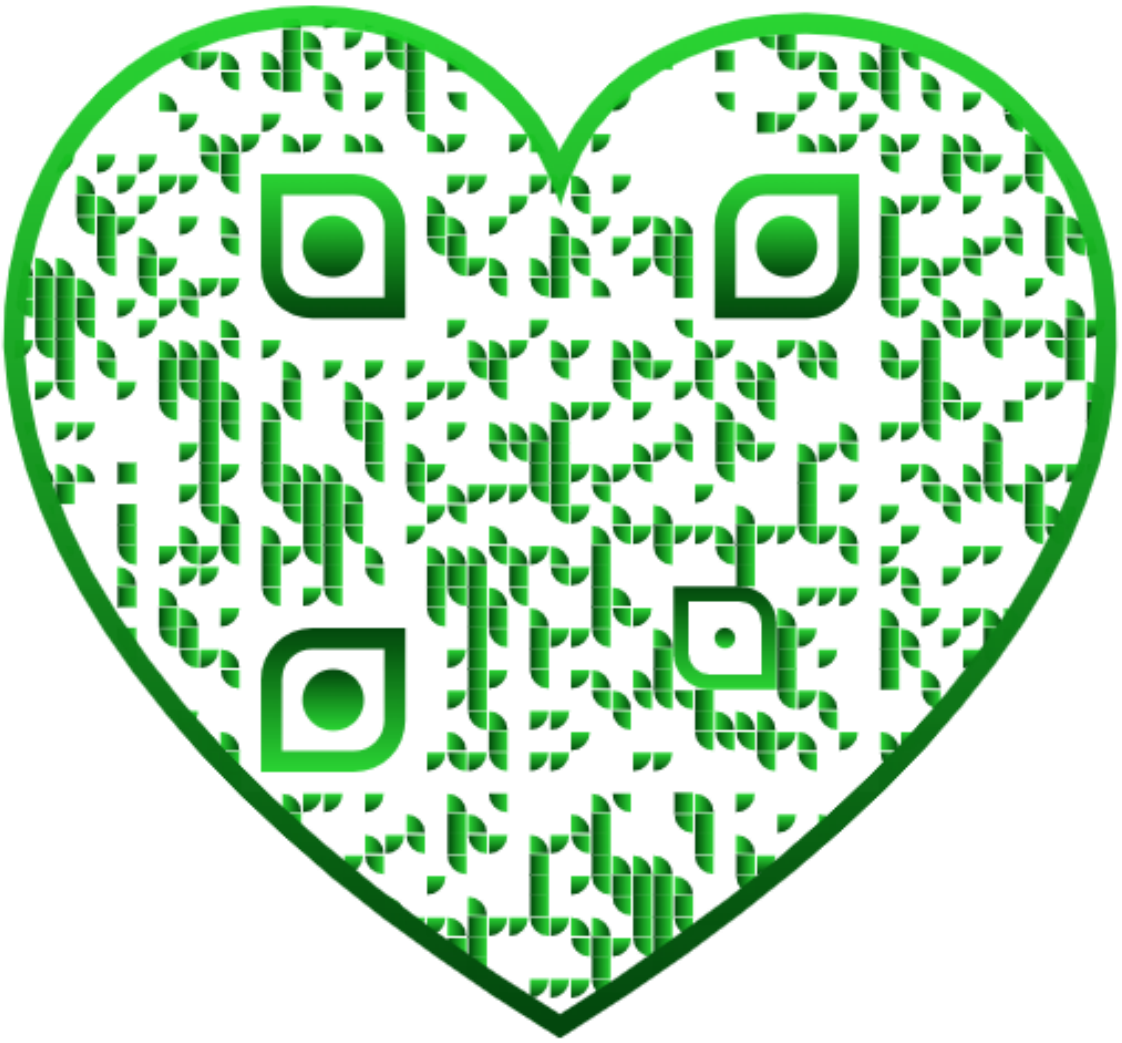
11.4a In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) **B** and is strongly recommended for those with severely increased albuminuria (UACR

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc25-SDIS.

Suggested citation: American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Care in Diabetes—2025. Diabetes Care 2025; 48(Suppl. 1):S239–S251

© 2024 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/journals/pages/license.



CKD is classified based on: • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer 3	Treat and refer 3	**Treat and refer 4+**
	G5	Kidney failure	<15	**Treat and refer 4+**	**Treat and refer 4+**	**Treat and refer 4+**

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 11.1—Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, and hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as should the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from de Boer et al. (1).

≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m^2 to maximally tolerated dose to prevent the progression of kidney disease and reduce cardiovascular events. **A**

11.4b Monitor for increased serum creatinine and for increased serum potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists (MRAs) are used, or for hypokalemia when diuretics are used at routine visits and 7–14 days after initiation or after a dose change. **B**

11.4c An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR. **A**

11.4d Continue renin-angiotensin system blockade for mild to moderate increases in serum creatinine (≤30%) in individuals who have no signs of extracellular fluid volume depletion. **A**

11.5a For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor with demonstrated benefit is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2. **A**

11.5b To reduce cardiovascular risk and kidney disease progression in people with type 2 diabetes and CKD, a glucagon-like peptide 1 agonist with demonstrated benefit in this population is recommended. **A**

11.5c To reduce cardiovascular events and CKD progression in people with CKD and albuminuria, a nonsteroidal MRA that has been shown to be effective in clinical trials is recommended (if eGFR is ≥25 mL/min/1.73 m^2). Potassium levels should be monitored. **A**

11.6 Potentially harmful antihypertensive medications in pregnancy should be avoided in sexually active individuals of childbearing potential who are not using reliable contraception and, if used, should be switched prior to conception to antihypertensive medications considered safer during pregnancy. **B**

11.7 Aim to reduce urinary albumin by ≥30% in people with CKD and albuminuria ≥300 mg/g to slow CKD progression. **B**

11.8 For people with non–dialysis-dependent stage G3 or higher CKD, protein intake should be 0.8 g/kg body weight per day, as for the general population. **A** For individuals on dialysis, protein intake of 1.0–1.2 g/kg/day should be considered since protein energy wasting is a major problem for some individuals on dialysis. **B**

11.9 Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m^2. **A**

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

11.10 Refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **B**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1). In this section, the focus is on CKD attributed to diabetes in adults, which occurs in 20–40% of people with diabetes (1–4). CKD in people with diabetes typically develops after a duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to kidney failure requiring dialysis or kidney transplantation and is the leading cause of end-stage kidney disease (ESKD) in the U.S. (5). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (6). For details on the management of CKD in children with diabetes, please see Section 14, "Children and Adolescents."

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urine albumin-to-creatinine ratio (UACR) in a random spot urine collection (1). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (7). Thus, semiquantitative or qualitative (dipstick) screening will need to be confirmed by UACR values in an accredited laboratory (8,9). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal level of urine albumin excretion is defined as $<$30 mg/g creatinine, moderately elevated albuminuria is defined as $\geq$30–300 mg/g creatinine, and severely elevated albuminuria is defined as $\geq$300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with kidney and cardiovascular outcomes (6,10,11). Furthermore, because of high biological variability of $>$20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3-to 6-month period should be abnormal before considering an individual to have moderately or severely elevated albuminuria (1,12,13). Exercise within 24 h, infection, fever, heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (14). Moreover, a recent analysis showed variability in the measurement of UACR when measured weekly over a 1-month period. Thus, repeated measurements and tracking of trending over time are needed to properly follow changes in UACR (12).

Traditionally, eGFR is calculated from serum creatinine using a validated formula (15). eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently $<$60 mL/min/1.73 m^2 and/or an urinary albumin value of $>$30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years (1,16). Historically, a correction factor for muscle mass was included in a modified equation for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms. Hence, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was refit without the race variable and should be used for everyone (17,18). Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF CHRONIC KIDNEY DISEASE IN PEOPLE WITH DIABETES

CKD in people with diabetes is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of CKD in people with diabetes is considered to include long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (2,3,16,19–21). An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For individuals with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for people with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (22). It cannot be definitively stated that a person with diabetes and CKD has CKD related to diabetes unless the person has a kidney biopsy, as there may be another cause or multiple causes. Hence, without a biopsy, it is recommended to state that the individual has CKD in a person with diabetes. In most people, there is no need for a kidney biopsy, as the other possible diagnoses would not change treatment. Referral to a nephrologist should be done if there are any reasons to consider another cause of CKD in a person with diabetes (**Table 11.1**).

STAGING OF CHRONIC KIDNEY DISEASE

Stage G1 and stage G2 CKD are defined by evidence of high albuminuria with eGFR $\geq$60 mL/min/1.73 m^2, and stages G3-G5 CKD are defined by progressively lower ranges of eGFR (23) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

Table 11.1—Reasons to consider nondiabetic kidney diseases in a person with chronic kidney disease and diabetes

- Type 1 diabetes duration <5 years
- Active urine sediment (e.g., containing red blood cells or cellular casts)
- Chronically well-managed blood glucose
- Rapidly declining eGFR
- Rapidly increasing or very high UACR or urine protein/creatinine level
- No retinopathy in a person with type 1 diabetes

Information adapted from Liang et al. (129). eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (6). Therefore, there is an additional subclassification by level of urine albumin (**Fig. 11.1**). Furthermore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex (1). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. Quantification of eGFR levels is essential for modifications of medication dosages or restrictions of use (**Fig. 11.1**) (23,24), and the degree of albuminuria should influence the choice of antihypertensive medications (see Section 10, "Cardiovascular Disease and Risk Management") or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (25).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (26,27). People with diabetes are at higher risk of AKI than those without diabetes (28). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), certain intravenous dyes (e.g., iodinated radiocontrast agents) and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized controlled trials of advanced kidney disease (29) or high CVD risk with normal kidney function (30–32). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression (33). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (34).

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (35). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrated that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (36,37). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (37).

Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose medications appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in individuals treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (38–40). Individuals with eGFR <60 mL/min/1.73 m^2 receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have their medication dosing verified, their exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and they should be evaluated for potential CKD complications (**Table 11.2**).

There is a clear need for annual quantitative assessment of UACR. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure goals. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR (41), and this also significantly affects cardiovascular risk. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitor or ARB therapy in people with type 2 diabetes, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved kidney and cardiovascular outcomes, leading to the recommendation that medications should be titrated to maximize reduction in UACR (8). See **Table 11.3** for interventions that lower albuminuria.

Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade (42). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (43,44).

The prevalence of CKD complications correlates with eGFR (40). When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.2**). Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESKD (see Section 4, "Comprehensive Medical Evaluation and Assessment of

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

Table 11.2—Screening for selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage G3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage G3 CKD, every 3–5 months for stage G4 CKD, and every 1–3 months for stage G5 CKD, or as indicated to evaluate symptoms or changes in therapy. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

Comorbidities," for further information on immunization).

Prevention

The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure management. There is no evidence that renin-angiotensin-aldosterone system inhibitors or any other interventions prevent the development of CKD in the absence of hypertension or albuminuria. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of CKD. In 2023, the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was published (45). This large prospective study compared liraglutide, sitagliptin, glimeperide, and insulin glargine with respect to achieving and maintaining A1C goals in people with type 2 diabetes treated with metformin monotherapy; kidney and cardiovascular end points were examined as secondary outcomes. A total of 5,047 participants were enrolled from July 2013 to August 2017 and were followed for an average of 5 years. Almost all participants did not have signs of kidney disease at the time of enrollment. No differences between the examined medications were observed, which suggests that there were no unique reno-protective effects among these medications for prevention. Of note, SGLT2 inhibitors were not included in the study, as these medications were not routinely available at the time the study started.

INTERVENTIONS

Nutrition

For people with stages 3–5 non–dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline (46). Some organizations recommend a lower protein intake (0.6–0.8 g/kg/day). In particular, guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) (47) and the International Society of Renal Nutrition and Metabolism (48) recommend a lower protein intake level for reno-protection and state that this lower level is relatively safe. However, for CKD in diabetes, the expert grade is "opinion" only. The guidelines note that the evidence for lower protein intake in people with CKD has been published for only those without diabetes, which is graded Level 1A. Low-protein eating patterns should only be followed alongside guidance from a health care professional experienced in managing nutrition for people with CKD.

Restriction of dietary sodium (to <2,300 mg/day) may be useful to manage blood pressure and reduce cardiovascular risk (49,50), and individualization of dietary potassium may be necessary to manage serum potassium concentrations (28,38–40). These interventions may be most important for individuals with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For individuals on dialysis, higher levels of dietary protein intake should be considered since protein-energy wasting is a major problem for some individuals on dialysis (51). Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Table 11.3—Interventions that lower albuminuria

- Blood glucose management
- Blood pressure management
- Treatment with ACE inhibitors or ARBs
- Smoking cessation
- Weight loss
- Changes in eating patterns (decreased salt intake and/or protein intake)
- Treatment with SGLT2 inhibitors, MRAs, or GLP-1 RAs

ARB, angiotensin receptor blocker; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MRA, mineralocorticoid receptor antagonist.

Glycemic Goals

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes (52,53) and type 2 diabetes (1,54–59). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C goals.

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

The presence of CKD affects the risks and benefits of intensive lowering of blood glucose and a number of specific glucose-lowering medications. Adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline (60). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (57,61,62). Therefore, in some people with prevalent CKD and substantial comorbidity, treatment may be less intensive (i.e., A1C goals may be higher) to decrease the risk of hypoglycemia (1,63). A1C levels are also less reliable at advanced CKD stages (64,65).

Blood Pressure and Use of ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors and ARBs remain a mainstay of management for people with CKD with albuminuria and for the treatment of hypertension in people with diabetes (with or without CKD in people with diabetes). Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal MRA effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

Hypertension is a strong risk factor for the development and progression of CKD (66). Antihypertensive therapy reduces the risk of albuminuria (67–70), and among people with type 1 or 2 diabetes with established CKD (eGFR $<$60 mL/min/1.73 m^2 and UACR $\geq$300 mg/g creatinine), ACE inhibitor or ARB therapy reduces the risk of progression to ESKD (71–80). Moreover, antihypertensive therapy reduces the risk of cardiovascular events (67).

A blood pressure level $<$130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes. Lower blood pressure goals (e.g., $<$130/80 mmHg) should be considered based on individual anticipated benefits and risks. People with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD; therefore, lower blood pressure goals may be suitable in some cases, especially in individuals with severely elevated albuminuria ($\geq$300 mg/g creatinine).

ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR $<$60 mL/min/1.73 m^2, and UACR $\geq$300 mg/g creatinine because of their proven benefits for prevention of CKD progression (71,72,74). ACE inhibitors and ARBs are considered to have similar benefits (75,76) and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria ($\geq$300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESKD (74,77). While ACE inhibitors or ARBs are often prescribed for moderately increased albuminuria (30–299 mg/g creatinine) without hypertension, outcome trials have not been performed in this setting to determine whether they improve kidney outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs among people with type 1 and type 2 diabetes who were normotensive with or without high albuminuria (formerly microalbuminuria, 30–299 mg/g creatinine) (78,79).

It should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of concerns that serum creatinine will rise. As previously noted, not maximizing these therapies for this reason would be considered suboptimal care. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR $<$30 mL/min/1.73 m^2 (80). Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued (36,81).

Two recent large retrospective analyses provide additional support for the aggressive use of ACE inhibitors and ARBs in individuals with CKD. Ku et al. (82) reviewed 17 trials that included 11,800 individuals with CKD (defined as eGFR $<$60 mL/min/1.73 m^2); 82% had diabetes. The authors reported that a $<$13% decline in eGFR over a 3-month period or a $<$21% decline in a 1-month period was associated with better long-term kidney outcomes. Hattori et al. (83) evaluated 6,065 participants between 2005 and 2021 (approximately 40% had diabetes) with eGFR ranging from 10 to 60 mL/min/1.73 m^2 who had ACE inhibitors or ARBs stopped (usually due to hyperkalemia or AKI) and found that those who restarted the ACE inhibitor or ARB had better long-term kidney outcomes and lower mortality (there was no significant difference in hyperkalemia in those who restarted ACE inhibitors or ARBs). There is also an accompanying editorial that details the strengths and weaknesses of the studies (84).

In the absence of kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (85). In a trial of people with type 2 diabetes and normal urinary albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (86). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of glomerulopathy assessed by kidney biopsy (78). This was further supported by a similar trial in people with type 2 diabetes (79).

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the medication combination had higher adverse event rates (hyperkalemia and/or AKI) (87,88). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Kidney Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (31,89–92). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by $>$50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

activity (92–94). Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) have also been shown to improve kidney outcomes (95–100). Kidney effects should be considered when selecting agents for glucose lowering (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease

For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia (101,102). Medication dosing may require modification with eGFR <60 mL/min/1.73 m^2 (1). **Figure 11.2** shows the American Diabetes Association and KDIGO consensus recommendation algorithm for medications in people with diabetes and CKD.

The FDA revised its guidance for the use of metformin in CKD in 2016 (103), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that *1*) metformin is contraindicated in individuals with an eGFR <30 mL/min/1.73 m^2, *2*) eGFR should be monitored while taking metformin, *3*) the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2 (104,105), *4*) metformin should not be initiated for individuals with an eGFR <45 mL/min/1.73 m^2, and *5*) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30–60 mL/min/1.73 m^2.

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as kidney protection from SGLT2 inhibitors and from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual's risks (cardiovascular and kidney in addition to glucose management) as well as considerations of effects on weight, other adverse effects, individual preferences, and cost.

SGLT2 inhibitors are recommended for people with eGFR ≥20 mL/min/1.73 m^2 and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management (106). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and slow progression of CKD (100,107–110).

A number of large cardiovascular outcomes trials in people with type 2 diabetes

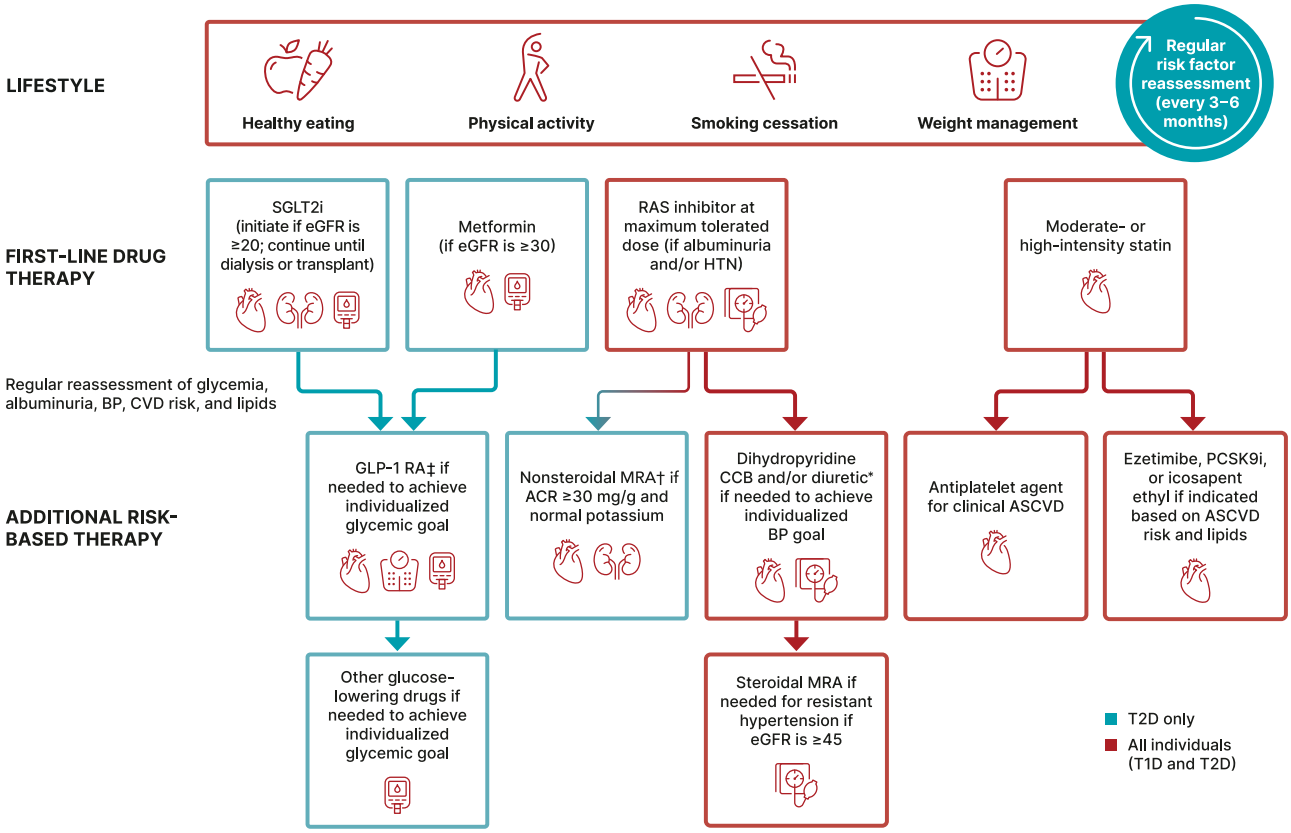

LIFESTYLE
Healthy eating
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
FIRST-LINE DRUG THERAPY
SGLT2i (initiate if eGFR is ≥20; continue until dialysis or transplant)
Metformin (if eGFR is ≥30)
RAS inhibitor at maximum tolerated dose (if albuminuria and/or HTN)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
ADDITIONAL RISK-BASED THERAPY
GLP-1 RA‡ if needed to achieve individualized glycemic goal
Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP goal
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic goal
Steroidal MRA if needed for resistant hypertension if eGFR is ≥45
T2D only
All individuals (T1D and T2D)

Figure 11.2—Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucose meter, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ‡Semaglutide can be used as another first-line agent for people with CKD. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Adapted from de Boer et al. (1).

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (91,95,98,111). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g creatinine, doubling of serum creatinine, ESKD, or death from ESKD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESKD, or death from ESKD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESKD, or death from ESKD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g creatinine, doubling of serum creatinine, or ESKD) by 36% (each $P <$ 0.01). These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of kidney effects as secondary outcomes.

Three large clinical trials of SGLT2 inhibitors have focused on people with CKD and assessment of primary kidney outcomes. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300–5,000 mg/g creatinine, and eGFR range 30–90 mL/min/1.73 m^2 (mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of >900 mg/day), had a primary composite end point of ESKD, doubling of serum creatinine, or renal or cardiovascular death (29,112). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESKD over control (29). Additionally, the development of the primary end point, which included dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the participants (29). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (29,110,113).

A second trial in advanced CKD in people with diabetes was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (114). This trial examined a cohort similar to that in CREDENCE except 67.5% of the participants had type 2 diabetes and CKD (the other one-third had CKD without type 2 diabetes), and the end points were slightly different. The primary outcome was time to the first occurrence of any of the components of the composite, including ≥50% sustained decline in eGFR or reaching ESKD or cardiovascular death, or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (≥50% sustained decline in eGFR or reaching ESKD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m^2 (range 25–75 mL/min/1.73 m^2) and a median UACR of 949 mg/g (range 200–5,000 mg/g). There was a significant benefit by dapagliflozin for the primary end point (hazard ratio [HR] 0.61 [95% CI 0.51–0.72]; $P <$ 0.001) (114). The HR for the kidney composite of a sustained decline in eGFR of ≥50%, ESKD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P <$ 0.001). The HR for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI 0.55–0.92; P = 0.009). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P <$ 0.004).

The most recently published clinical trial was EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) (115). This study enrolled participants with kidney disease with an eGFR of at least 20 but less than 45 mL/min/1.73 m^2 or who had an eGFR of at least 45 but less than 90 mL/min/1.73 m^2 with a UACR of at least 200 mg/g creatinine. Approximately one-half of the 6,609 participants had diabetes. The empagliflozin-treated participants had lower risk of progression of kidney disease and lower risk of death from cardiovascular causes (HR 0.72 [95% CI 0.64–0.82]; $P <$ 0.001).

With respect to cardiovascular outcomes, SGLT2 inhibitors have demonstrated reduced risk of heart failure hospitalizations and some also demonstrated cardiovascular risk reduction. GLP-1 RAs have clearly demonstrated cardiovascular benefits. (See Section 10, "Cardiovascular Disease and Risk Management," for further detailed discussion.)

Of note, while the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen at eGFR levels as low as 20 mL/min/1.73 m^2 even with no significant change in glucose (29,31,52,63,98,111,114–116). Most participants with CKD in these trials also had diagnosed atherosclerotic cardiovascular disease (ASCVD) at baseline, although ∼28% of CANVAS participants with CKD did not have diagnosed ASCVD (32).

Based on evidence from the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials, as well as secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in individuals with an eGFR of 20 mL/min/1.73 m^2, independent of glucose-lowering effects (110,113).

The recently published FLOW study demonstrated that the GLP-1 RA semaglutide had reno-protective effects in people with CKD (100). The study enrolled 3,533 participants with significant kidney disease defined by level of eGFR and/or by level of albuminuria (of note, all participants had an albuminuria level of at least 100 mg/g). The primary outcome was defined as the first major kidney disease event (onset of >50% in eGFR, onset of persistent eGFR of <15 mL/min/1.73 m^2, initiation of dialysis or transplant, renal death, and cardiovascular death). The study was stopped early due to reaching a prespecified outcome. There was a 24% lower HR for those taking semaglutide compared with the placebo group. Of note, cardiovascular deaths

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

comprised about 38% of the events. When the cardiovascular deaths are removed from the analysis, the HR for kidney specific events was 21% lower in those taking semaglutide. Thus, the study supports a beneficial effect of semaglutide in slowing decline in kidney function as well as being cardioprotective in people with CKD and type 2 diabetes. Of note, the participants who took semaglutide had lower A1C, lower blood pressure, and more weight loss—all of which are beneficial for slowing decline in kidney function and reducing cardiovascular adverse events. Whether this beneficial combination of effects was the primary cause for the renoprotective outcomes or whether there is a unique reno-protective effect of semaglutide remains to be determined.

Adverse event profiles of these agents also must be considered. Please refer to **Table 9.2** for medication-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in people with CKD are ongoing and will be reported in the next few years.

For people with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors are recommended for individuals at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.3**). For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor in individuals with eGFR $\geq$20 mL/min/1.73 m^2 is recommended to reduce CKD progression and cardiovascular events. The reason for the limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for CKD in people with diabetes are CREDENCE, DAPA-CKD, and EMPA-KIDNEY. CREDENCE enrollment criteria included eGFR $>$30 mL/min/1.73 m^2 and UACR $>$300 mg/g (29,110). DAPA-CKD enrolled individuals with eGFR $>$25 mL/min/1.73 m^2 and UACR $>$200 mg/g. Subgroup analyses from DAPA-CKD (117) and analyses from the EMPEROR heart failure trials suggest that SGLT2 inhibitors are safe and effective at eGFR levels of $>$20 mL/min/1.73 m^2. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) enrolled 5,998 participants (118), and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled 3,730 participants (119); enrollment criteria included eGFR $>$60 mL/min/1.73 m^2, but efficacy was seen at eGFR $>$20 mL/min/1.73 m^2 in people with heart failure. Most recently, the EMPA-KIDNEY trial showed efficacy in participants with eGFR as low as 20 mL/min/1.73 m^2 (115). Hence, the new recommendation is to use SGLT2 inhibitors in individuals with eGFR as low as 20 mL/min/1.73 m^2. In addition, the DECLARE-TIMI 58 trial suggested effectiveness in participants with normal urinary albumin levels (120). In sum, for people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in people with an eGFR $\geq$20 mL/min/1.73 m^2.

Of note, GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment (121).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in people with diabetes and CKD because of the risk of hyperkalemia (122,123). However, data that do exist suggest sustained benefit on albuminuria reduction. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (124). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the kidney effects of finerenone, demonstrated a significant reduction in CKD progression and cardiovascular events in people with diabetes and advanced CKD (33,125). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR $>$40% from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point of cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and change in UACR from baseline to month 4, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of $\geq$57% from baseline over at least 4 weeks, or renal death.

The double-blind, placebo-controlled trial randomized 5,734 people with CKD and type 2 diabetes to receive finerenone, a nonsteroidal MRA, or placebo. Eligible participants had a UACR of 30 to $<$300 mg/g, an eGFR of 25 to $<$60 mL/min/1.73 m^2, and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to $<$75 mL/min/1.73 m^2. The potassium level had to be $\leq$4.8 mmol/L. The mean age of participants was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m^2, and the mean albuminuria was 852 mg/g (interquartile range 446–1,634 mg/g). The primary end point was reduced with finerenone compared with placebo (HR 0.82 [95% CI 0.73–0.93]; P = 0.001), as was the key secondary composite of cardiovascular outcomes (HR 0.86 [95% CI 0.75–0.99]; P = 0.03). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed, and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial assessed the safety and efficacy of finerenone in reducing cardiovascular events among people with type 2 diabetes and CKD with elevated UACR (30 to $<$300 mg/g creatinine) and eGFR 25–90 mL/min/1.73 m^2 (126). The potassium level had to be $\leq$4.8 mmol/L The study randomized eligible subjects to either finerenone (n = 3,686) or placebo (n = 3,666). Participants with an eGFR of 25–60 mL/min/1.73 m^2 at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was $\geq$60 mL/min/1.73 m^2, the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was $\leq$4.8 mmol/L and eGFR was stable. The mean age of participants was 64.1 years (31% were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, the mean systolic blood pressure was 136 mmHg, and the mean GFR was 67.8 mL/min/1.73 m^2. People with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary end point compared with the placebo group (12.4% vs. 14.2%; HR 0.87 [95% CI 0.76–0.98]; *P* = 0.03). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% in the placebo group (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in ESKD: 0.9% vs. 1.3% in the placebo group (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia in the finerenone group, 10.8% vs. 5.3%, although only 1.2% of the 3,686 individuals on finerenone stopped the study due to hyperkalemia.

The FIDELITY prespecified pooled efficacy and safety analysis incorporated individuals from both the FIGARO-DKD and FIDELIO-DKD trials (*N* = 13,171) to allow for evaluation across the spectrum of severity of CKD, since the populations were different (with a slight overlap) and the study designs were similar (127). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure for finerenone vs. placebo (12.7% vs. 14.4%; HR 0.86 [95% CI 0.78–0.95]; *P* = 0.0018).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.670.88]; *P* = 0.0002).

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and kidney outcomes with finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

Of note, there has not been a direct comparison of MRAs and SGLT2 inhibitors. At this time, they can be used interchangeably or together for the goal of slowing progression of CKD and providing cardiovascular protection. There have also been no studies directly comparing MRAs, SGLT2 inhibitors, and GLP-1 RAs. Health care professionals should use their best judgement as to which medication to prescribe initially and in combination. As noted, all of these studies included participants taking either an ACE inhibitor or an ARB, often at maximally tolerated doses.

REFERRAL TO A NEPHROLOGIST

Health care professionals should consider referral to a nephrologist if the individual with diabetes has continuously rising UACR levels and/or continuously declining eGFR, if there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria despite good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESKD (1). The threshold for referral may vary depending on the frequency with which a health care professional encounters people with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (128).

However, other specialists and health care professionals should also educate people with diabetes about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

References

1. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022;45:3075–3090
2. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
3. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–2539
4. DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:24–30
5. Johansen KL, Chertow GM, Foley RN, et al. US Renal Data System 2020 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2021;77:A7–A8
6. Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–1673
7. Yarnoff BO, Hoerger TJ, Simpson SK, et al.; Centers for Disease Control and Prevention CKD Initiative. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. BMC Nephrol 2017;18:85
8. Coresh J, Heerspink HJL, Sang Y, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol 2019;7:115–127
9. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis 2020;75:84–104
10. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–308
11. Groop P-H, Thomas MC, Moran JL, et al.; FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009;58:1651–1658
12. Rasaratnam N, Salim A, Blackberry I, et al. Urine albumin-creatinine ratio variability in people with type 2 diabetes: clinical and research implications. Am J Kidney Dis 2024;84:8–17.e1
13. Naresh CN, Hayen A, Weening A, Craig JC, Chadban SJ. Day-to-day variability in spot urine albumin-creatinine ratio. Am J Kidney Dis 2013;62:1095–1101
14. Tankeu AT, Kaze FF, Noubiap JJ, Chelo D, Dehayem MY, Sobngwi E. Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes. World J Nephrol 2017;6:209–216
15. Delanaye P, Glassock RJ, Pottel H, Rule AD. An age-calibrated definition of chronic kidney disease: rationale and benefits. Clin Biochem Rev 2016;37:17–26
16. Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
17. Inker LA, Eneanya ND, Coresh J, et al.; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385:1737–1749
18. Miller WG, Kaufman HW, Levey AS, et al. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: practical guidance for clinical laboratories. Clin Chem 2022;68:511–520
19. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

Complications study. Diabetes Care 2010;33:1536–1543
20. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia 2013;56:457–466
21. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function-even without albuminuria. Diabetes Care 2019;42:1886–1894
22. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–147
23. Matzke GR, Aronoff GR, Atkinson AJ, Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:1122–1137
24. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014;311:2518–2531
25. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M, Sequist TD, National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical approach to detection and management of chronic kidney disease for the primary care clinician. Am J Med 2016;129:153–162.e157
26. Zhou J, Liu Y, Tang Y, et al. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. Int Urol Nephrol 2016;48:125–132
27. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol 2018;14:607–625
28. James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis 2015;66:602–612
29. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
30. Nadkarni GN, Ferrandino R, Chang A, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 2017;40:1479–1485
31. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
32. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. Circulation 2018;138:1537–1550
33. Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–2229
34. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011;6:2567–2572
35. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160:685–693
36. Collard D, Brouwer TF, Peters RJG, Vogt L, van den Born B-JH. Creatinine rise during blood pressure therapy and the risk of adverse clinical outcomes in patients with type 2 diabetes mellitus. Hypertension 2018;72:1337–1344
37. Malhotra R, Craven T, Ambrosius WT, et al.; SPRINT Research Group. Effects of intensive blood pressure lowering on kidney tubule injury in CKD: a longitudinal subgroup analysis in SPRINT. Am J Kidney Dis 2019;73:21–30
38. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. Clin J Am Soc Nephrol 2017;12:245–252
39. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. J Am Heart Assoc 2017;6
40. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. Int J Cardiol 2017;245:277–284
41. Zelniker TA, Raz I, Mosenzon O, et al. Effect of dapagliflozin on cardiovascular outcomes according to baseline kidney function and albuminuria status in patients with type 2 diabetes: a prespecified secondary analysis of a randomized clinical trial. JAMA Cardiol 2021;6:801–810
42. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care 2015;21:S212–220
43. de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC study. Clin J Am Soc Nephrol 2016;11:1969–1977
44. Sumida K, Molnar MZ, Potukuchi PK, et al. Changes in albuminuria and subsequent risk of incident kidney disease. Clin J Am Soc Nephrol 2017;12:1941–1949
45. Wexler DJ, de Boer IH, Ghosh A, et al.; GRADE Research Group. Comparative effects of glucose-lowering medications on kidney outcomes in type 2 diabetes: the GRADE randomized clinical trial. JAMA Intern Med 2023;183:705–714
46. Klahr S, Levey AS, Beck GJ, et al.; Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994;330:877–884
47. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis 2020;76:S1–S107
48. Rhee CM, Wang AY-M, Biruete A, et al. Nutritional and dietary management of chronic kidney disease under conservative and preservative kidney care without dialysis. J Ren Nutr 2023;33:S56–S66
49. Mills KT, Chen J, Yang W, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA 2016;315:2200–2210
50. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269–1324
51. Murray DP, Young L, Waller J, et al. Is dietary protein intake predictive of 1-year mortality in dialysis patients? Am J Med Sci 2018;356:234–243
52. DCCT/EDIC Research Group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
53. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
54. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
55. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
56. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
57. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
58. Zoungas S, Arima H, Gerstein HC, et al.; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–437
59. Agrawal L, Azad N, Bahn GD, et al.; VADT Study Group. Long-term follow-up of intensive glycaemic control on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). Diabetologia 2018;61:295–299
60. Papademetriou V, Lovato L, Doumas M, et al.; ACCORD Study Group. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int 2015;87:649–659
61. Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int 2013;83:517–523
62. Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. Diabetes Care 2016;39:694–700

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

63. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–886
64. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
65. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102: S1–S127
66. Leehey DJ, Zhang JH, Emanuele NV, et al.; VA NEPHRON-D Study Group. BP and renal outcomes in diabetic kidney disease: the Veterans Affairs Nephropathy in Diabetes Trial. Clin J Am Soc Nephrol 2015;10:2159–2169
67. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
68. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
69. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
70. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
71. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
72. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–1462
73. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
74. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355: 253–259
75. Barnett AH, Bain SC, Bouter P, et al.; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351: 1952–1961
76. Wu H-Y, Peng C-L, Chen P-C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers for major renal outcomes in patients with diabetes: a 15-year cohort study. PLoS One 2017; 12:e0177654
77. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–878
78. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51
79. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 2013;67:532–3231
80. Qiao Y, Shin J-I, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med 2020;180:718–726
81. Ohkuma T, Jun M, Rodgers A, et al.; ADVANCE Collaborative Group. Acute increases in serum creatinine after starting angiotensin-converting enzyme inhibitor-based therapy and effects of its continuation on major clinical outcomes in type 2 diabetes mellitus. Hypertension 2019;73:84–91
82. Ku E, Tighiouart H, McCulloch CE, et al. Association between acute declines in eGFR during renin-angiotensin system inhibition and risk of adverse outcomes. J Am Soc Nephrol 2024;35:1402–1411
83. Hattori K, Sakaguchi Y, Oka T, et al. Estimated effect of restarting renin-angiotensin system inhibitors after discontinuation on kidney outcomes and mortality. J Am Soc Nephrol 2024; 35:1391–1401
84. Shulman R, Cohen JB. Navigating renin-angiotensin system inhibitors in patients with declines in eGFR. J Am Soc Nephrol 2024;35: 1309–1311
85. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438
86. Haller H, Ito S, Izzo JL, Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–917
87. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
88. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892–1903
89. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014; 129:587–597
90. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 2017;28: 368–375
91. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
92. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:1845–1855
93. Woods TC, Satou R, Miyata K, et al. Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. Am J Nephrol 2019;49:331–342
94. Heerspink HJL, Perco P, Mulder S, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia 2019;62:1154–1166
95. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
96. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. Am J Kidney Dis 2015;66:441–449
97. Mann JFE, Ørsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017;377:839–848
98. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
99. Shaman AM, Bain SC, Bakris GL, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. Circulation 2022;145: 575–585
100. Perkovic V, Tuttle KR, Rossing P, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109–121
101. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med 2017;177: 1461–1470
102. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121–1127
103. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2017. Accessed 25 August 2024. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain
104. Lalau J-D, Kajbaf F, Bennis Y, Hurtel-Lemaire A-S, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. Diabetes Care 2018;41:547–553
105. Chu PY, Hackstadt AJ, Chipman J, et al. Hospitalization for lactic acidosis among patients with reduced kidney function treated with metformin or sulfonylureas. Diabetes Care 2020; 43:1462–1470
106. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–158
107. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024

receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139:2022–2031
108. Mann JFE, Hansen T, Idorn T, et al. Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a post-hoc analysis of the SUSTAIN 1-7 randomised controlled trials. Lancet Diabetes Endocrinol 2020;8:880–893
109. Mann JFE, Muskiet MHA. Incretin-based drugs and the kidney in type 2 diabetes: choosing between DPP-4 inhibitors and GLP-1 receptor agonists. Kidney Int 2021;99:314–318
110. Bakris GL. Major advancements in slowing diabetic kidney disease progression: focus on SGLT2 inhibitors. Am J Kidney Dis 2019;74:573–575
111. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
112. Jardine MJ, Mahaffey KW, Neal B, et al.; CREDENCE study investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. Am J Nephrol 2017;46:462–472
113. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. Circulation 2019;140:739–750
114. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–1446
115. Herrington WG, Staplin N, Wanner C, et al.; The Empa-Kidney Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117–127
116. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357
117. Chertow GM, Vart P, Jongs N, et al.; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin in stage 4 chronic kidney disease. J Am Soc Nephrol 2021;32:2352–2361
118. Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–1461
119. Packer M, Anker SD, Butler J, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–1424
120. Mosenzon O, Wiviott SD, Heerspink HJL, et al. The effect of dapagliflozin on albuminuria in DECLARE-TIMI 58. Diabetes Care 2021;44:1805–1815
121. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. Diabetes Ther 2019;10:5–19
122. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis 2008;51:199–211
123. Sarafidis P, Papadopoulos CE, Kamperidis V, Giannakoulas G, Doumas M. Cardiovascular protection with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in chronic kidney disease: a milestone achieved. Hypertension 2021;77:1442–1455
124. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J 2021;42:152–161
125. Filippatos G, Anker SD, Agarwal R, et al.; FIDELIO-DKD Investigators. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. Circulation 2021;143:540–552
126. Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–2263
127. Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474–484
128. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. Cochrane Database Syst Rev 2014:CD007333
129. Liang S, Zhang X-G, Cai G-Y, et al. Identifying parameters to distinguish non-diabetic renal diseases from diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. PLoS One 2013;8:e64184

Downloaded from http://diabetesjournals.org/care/article-pdf/48/Supplement_1/S239/791464/dc25s011.pdf by guest on 11 December 2024